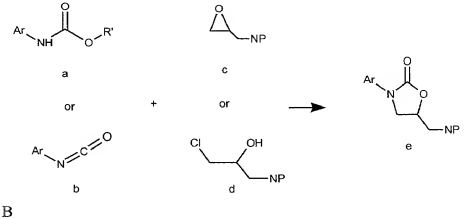
Similarly, the following references disclose variations of the reaction of a carbamate with glycidyl butyrate: *Abstracts of Papers*, 206th National Meeting of the American Chemical Society, Chicago, IL, August, 1993; American Chemical Society: Washington, DC, 1993; ORGN 089; *J. Med. Chem.*, *39*, 673 (1996); *J. Med. Chem., 39*, 680 (1996); International Publications WO93/09103, WO93/23384, WO95/07271, WO96/13502, and WO96/15130; *Abstracts of Papers*, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1995; American Society for Microbiology: Washington, DC, 1995, Abstract No. F208; *Abstracts of Papers*, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1995; American Society for Microbiology: Washington, DC, 1995, Abstract No. F207; *Abstracts of Papers*, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1995; American Society for Microbiology: Washington, DC, 1995, Abstract No. F206; *Abstracts of Papers*, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September, 1995; and American Society for Microbiology: Washington, DC, 1995, Abstract No. F227. The disclosed reactions use either *n*-butyllithium, lithium diisopropylamide, or lithium hexamethyldisilazide as the base to generate the nucleophilic anion or the carbamate over a temperature range of -78°C to -40°C, followed by addition of the glycidyl butyrate at -78°C, and warming to 20-25°C to produce the 5-(R)-hydroxymethyl-oxazolidinones wherein the ester is cleaved during the reaction.

As stated previously, the 5-(R)-hydroxymethyl-oxazolidinones then are aminated and acylated in subsequent steps. For example, International Publication WO95/07271 discloses the ammonolysis of 5-(R)-methylsulfonyloxymethyl-oxazolidinones. Likewise, U.S. Patent No. 4,476,136 discloses a method of transforming 5-hydroxymethyl-oxazolidinones to the corresponding 5-(S)-aminomethyl-oxazolidinones (X) by treatment with methanesulfonyl chloride, followed by potassium phthalimide, then followed by hydrazine. *J. Med. Chem.*, *32*, 1673 (1989) and *Tetrahedron, 45*, 1323 (1989) disclose a method of transforming 5-hydroxymethyl-oxazolidinones into the corresponding 5-(S)-acetamidomethyl-

oxazolidinones by treating with methanesulfonyl chloride or tosyl chloride, followed by the stepwise addition of sodium azide, trimethylphosphite, or platinum dioxide/hydrogen, and acetic anhydride or acetyl chloride to give the desired 5-(S)-acetamidomethyl-oxazolidinone. Likewise, U.S. provisional application Serial No. 60/015,499 discloses a method of preparing 5-(S)-hydroxymethyl-oxazolidinone intermediates, as well as a process to convert these intermediates into 5-aminomethyl-oxazolidinone intermediates which can be acylated to produce pharmacologically active 5-(S)-acetamidomethyl-oxazolidinones. U.S. Patent No. 3,654,298 discloses the synthesis of 5-alkoxymethyl-3-aryl-oxazolidinones by sodium ethoxide induced cyclization of chlorocarbamates.

The second method (Scheme B) involves condensation of an aromatic carbamate (a) or isocyanate (b) with a protected nitrogen (NP)-containing three-carbon reagent to provide an oxazolidinone having the desired amine functionality at the 5-position (e). For example, *J. Med. Chem.*, *33*, 2569 (1990)



Scheme B

discloses the condensation of an isocyanate (b) with racemic glycidyl azide (c, NP $=N_3$) to provide a racemic 5-azidomethyl-oxazolidinone (e). Two subsequent steps are required to convert the racemic azidomethyl-oxazolidinone into a racemic 5-acetamidomethyl-oxazolidinone (e, NP = NHAc), which has antibiotic activity.

International Publication WO99/24393 discloses the reaction of a benzylcarbamoyl amine with three carbon reagents containing amines (NP = NH_2), acetamides (NP = NHAc), benzalimines (NP = N=C-Ph), or phthalimides. Likewise, *Tetrahedron Letters*, 37, 7937-40 (1996) discloses a synthesis of acetamidomethyl-oxazolidinones involving the process of condensing a carbamate with 1.1 equivalents of *n*-butyl lithium (tetrahydrofuran (THF), -78°C), followed by 2 equivalents of S-glycidylacetamide (a, NP = -NHAc), to give the corresponding 5-(S)-acetamidomethyl-oxazolidinone (e). The S-glycidylacetamide can be made by the procedure disclosed in Jacobsen et. al., *Tet. Lett. 37*, 7937 (1996).

The S-enantiomer of epoxide (c) (Scheme B, NP = $NHCO_2$t-Bu) is well known in the literature, and has been used to prepare oxazolidinones as disclosed in International Publications WO 99/40094 and WO 99/3764, and German Patent application DE 19802239 A1, although by different routes than that shown in Scheme B. The (S)-epoxide (c) has been prepared by a hydrolytic kinetic resolution of the racemic epoxide as disclosed in WO 00/09463, and from R-glycidol as disclosed in WO 93/01174 and *J. Med. Chem., 37*, 3707 (1994). However, the (S)-epoxide has not been prepared in crystalline form.

The prior art is silent with respect to the use of carbamates (a) or isocyanates (b) in condensations with tert-butylcarbamoyl-, (BOC), or other carbamoyl-protected nitrogen-containing three-carbon reagents (c,d, NP =NCOOR") to directly form oxazolidinones (e). The present invention involves condensation of a carbamate with a carbamoyl-protected derivative of glycidylamine or 3-amino-1-halo-2-propanol. The use of the carbamoyl protecting group, and specifically a tert-butylcarbamoyl (BOC) protecting group, results in a more facile reaction, with a greater yield, compared to the prior art. For example, the analogous acetamide reaction (Scheme B, NP = NHAc) typically requires the use of two equivalents of this reagent for the condensation to occur. In contrast, only 1.3 equivalents of the tert-butylcarbamoyl reagent (Scheme B, NP = NHBOC) is required to obtain comparable yields. The success of such a carbamate condensation is both surprising and unexpected because of the apparent steric hindrance of the tert-butylcarbamoyl group.